A Medicine to Control Bilharzia
Part 2: Developing a medicine to control bilharzia

Contents: Reading, questions and discussion concerning the development, testing and production of a pharmaceutical product for the control of a tropical disease.

Time: 1 to 2 periods, depending on amount of discussion.

Intended use: GCSE Chemistry, Biology and Integrated Science. Links with work on carbon compounds in chemistry, and work on disease control in biology.

Aims:

- To complement work on carbon compounds and on disease
- To develop awareness of the scale and impact of a major tropical disease
- To show the stages by which a pharmaceutical product is developed, through synthesis, testing and safety screening to a large-scale manufacture
- To provide opportunities to practise skills in reading and comprehension, and to encourage readiness to enter into discussion.

Requirements: Students worksheets No. 305

This passage of reading and associated notes could be done for homework or in class. The advantage of class use is that students could discuss some of the questions in small groups.

Notes on some of the questions

Qs 2 and 3 'Compound X' differs from 'Compound A' only in the presence of an OH group on the methyl group attached to the benzene ring. The hydroxylation of this group and no other is difficult to achieve chemically. In practice a biological fermentation method is used.

Qs 4 to 7 and 14 Many children have strong feelings about the use of animals in research. Attempts are being made to find alternatives to animal testing, for example, using cell cultures. But the problem is that once inside the body, medicines undergo many complex metabolic changes. It is difficult to see the whole picture of the medicine's effects without testing the medicine on whole live animals. The majority of experiments are done on mice, but to get a good idea of the behaviour of a medicine in humans, it is desirable to test it on other animals, like rabbits, cats, dogs and monkeys, which are closer to humans. Medicines are not tested on humans until their safety has been demonstrated to an acceptable level in several species.

Q.8 Medicines are tested on healthy people first because they are better able than sick people to sustain any unexpected side-effects.

Q.10 The proportion of para-toluidine converted to Compound X would be $(0.5)^6 = 0.015625$. Thus to produce 1 molecule of Compound X, $1/015625 = 64$ molecules of para-toluidine are needed.

Q.12 This question is intended to bring out the problem of developing sophisticated pharmaceuticals in a country with a small scientific and technological base.

Acknowledgements Figure 1 adapted from *Manson's Tropical Diseases* (18th edn) by P.E.C. Manson-Bahr and F.I.C. Apted (Bailliere Tindall); Figure 5: photo provided by Pfizer Central Research.

A MEDICINE TO CONTROL BILHARZIA — Part 2

What is bilharzia?

This unit is about a disease which is very common in tropical countries. Doctors call the disease **schistosomiasis** or **bilharzia**. It is sometimes called 'snail fever', because water snails play a part in spreading the disease.

The map in Figure 1 shows the parts of the world where bilharzia is common. You can see that most of the countries affected are in the poorer, developing parts of the world.

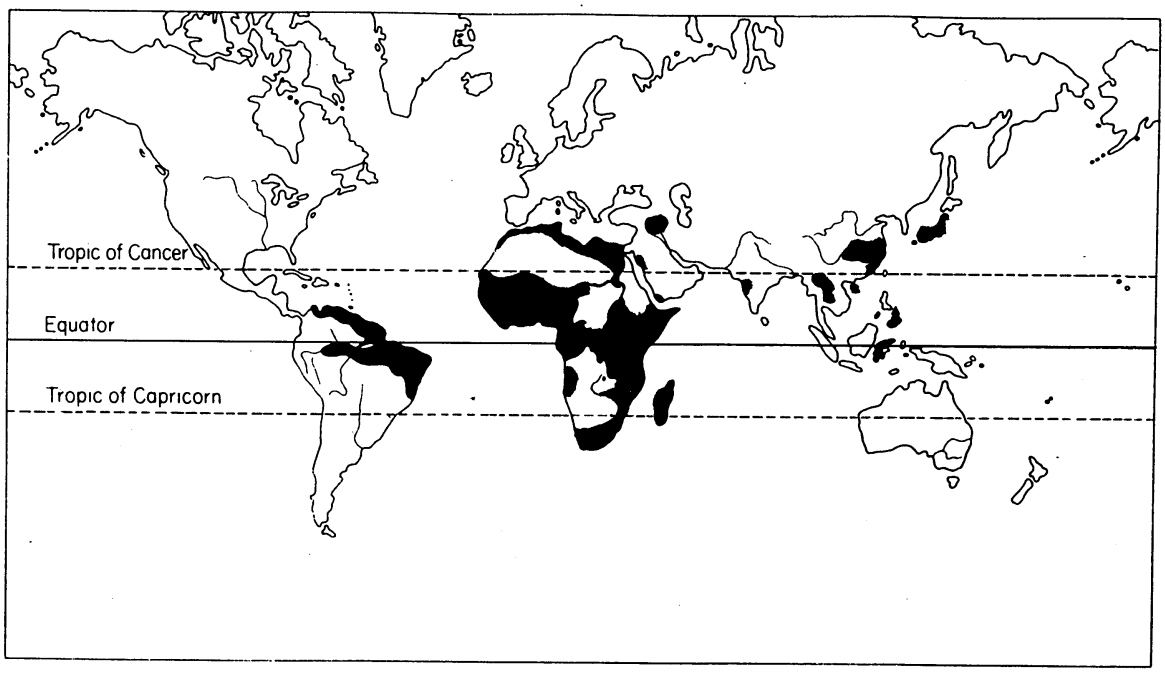

Figure 1 The parts of the world where bilharzia occurs are shown in black

Doctors believe that throughout the world about 200 million people are infected with bilharzia. This is nearly one in 20 of the world's population.

Bilharzia does not often kill, but it weakens the sufferers and makes them lethargic and short of energy. The symptoms of the disease include a swollen abdomen, diarrhoea and loss of blood. Because adult sufferers feel lethargic, it is hard for them to work. This makes it difficult for them to support their families. In some communities, 95 per cent of the population may be infected. This drags down the whole community.

This unit looks at how a particular medicine was developed to control bilharzia. Unit 304, *A Medicine to Control Bilharzia — Part 1*, looks at the causes of the disease, and different ways of controlling it.

Developing a medicine to control bilharzia

If you have used *A Medicine to Control Bilharzia — Part 1*, you will know that bilharzia is caused by a blood fluke. This parasite lives in the victim's blood vessels. There are several ways of controlling the disease. An important way is to give the patient a medicine which kills or paralyses the blood flukes. This part of the unit is about the development of such a medicine, called 'Compound X'.

The stages in developing a new medicine

Medicines are made by pharmaceutical companies. As well as making medicines, pharmaceutical companies are always trying to develop new ones. Developing new medicines takes a long time. Compound X took over ten years to develop. One of the main reasons for this is the need to test any new medicine very carefully. First the medicine must be tested to make sure it works and controls the disease in the laboratory. It must also be tested to make sure it is safe and does not have any serious side-effects. These tests are done on animals first, then humans.

The main stages in developing a new medicine are shown in Figure 2. In fact several of these stages overlap.

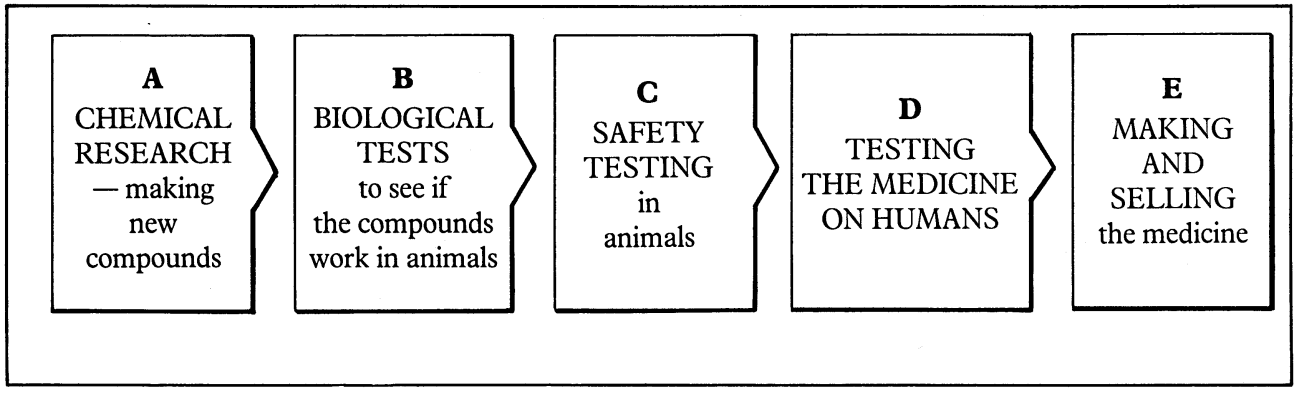

Figure 2 The main stages in developing a new medicine

A Chemical research

All medicines are chemical compounds. Almost all of them are organic compounds, containing carbon and hydrogen. In looking for a medicine to cure bilharzia, the trick is to look for compounds that will poison blood flukes but will not harm humans.

When the search began, some medicines already existed for treating bilharzia. But they had disadvantages — mainly in the form of unpleasant side-effects.

Chemists began by making compounds that were similar to one of the medicines already being used. These compounds were given to laboratory mice which were suffering from bilharzia. One compound, which we will call 'Compound A', was found to be very good at controlling the disease in mice.

The chemical structure of 'Compound A' is shown in Figure 3. Answer question 1.

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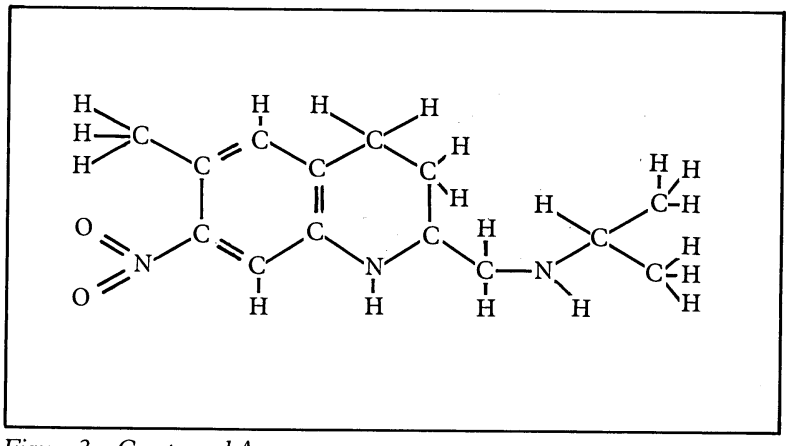

Figure 3 Compound A

Question

1 *What is the molecular formula of Compound A? (The molecular formula gives the number of each type of atom, but not their arrangement. For example, the molecular formula of sulphuric acid is H_2SO_4.)*

B Biological tests

Compound A was promising, so more investigations were made on it. Biological tests showed that it was not actually Compound A itself that was active in controlling the disease.

Once a medicine has been taken by a patient, it is metabolized. This means chemical changes happen to it inside the patient's body. More tests on animals showed that Compound A was changed to a new substance in the liver. We will call this new substance 'Compound X'. Compound X is the active compound that poisons the blood flukes.

The chemical structure of Compound X is shown in Figure 4. Answer questions 2 and 3.

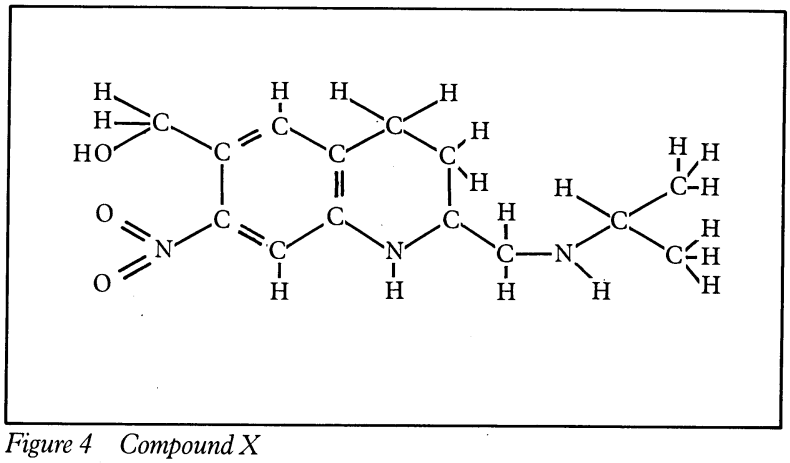

Figure 4 Compound X

Questions

2 *Look closely at the structure of Compound X. Compare it with Compound A. What difference is there between the two compounds?*

3 *What would chemists have to do to turn Compound A into Compound X? Why might this be difficult? (We will return to this question when we look at the manufacture of the medicine.)*

Compound X was so effective at controlling the disease in the laboratory that it was decided to test it further. Many more biological tests had to be done, to find out what would happen to Compound X in the patient's body. At this stage the medicine had not yet been tested in humans, only in animals. Before it could be tried in humans, it had to be tested for safety.

C Safety testing

Some medicines have side-effects that only show after a long time. Safety studies therefore have to be carried out over several years.

The medicine is first given to animals. It is given in doses far greater than would be given to humans. The animals are then checked for side-effects. Safety tests are first carried out in mice. If the tests on mice are successful, the medicine is tested in larger animals such as monkeys.

Of course the animals may suffer during the safety tests. All animal testing laboratories are frequently visited by government inspectors. These inspectors check to see there is no unnecessary suffering.

After the tests, the animals are usually killed and examined to find out what effect the medicine has had on different organs.

Answer questions 4 to 7.

Questions

4 *Why are the first safety tests done on animals, not humans?*

5 *Why are mice used before larger animals?*

6 *Why can scientists find out more by testing in monkeys than by testing in mice?*

7 *Are there other ways, not using animals, that medicines could be tested for safety?*

D Testing the medicine in humans

The only way of making sure a medicine is safe and effective is to test it in humans. After Compound X had passed the animal safety tests, it was tested on healthy human volunteers who were not suffering from bilharzia. The volunteers are given small doses at first, which are gradually increased.

If these first human tests are successful, the medicine goes for clinical trials. In the case of Compound X, this meant giving the medicine to people who were actually suffering from bilharzia. Doctors follow these trials carefully, to check how well the medicine works, and whether it has side-effects. Only after successful clinical trials can the medicine get a licence which allows it to be sold.

Answer questions 8 and 9.

Questions

8 *Why is the medicine tested in healthy people before it is used in patients?*

9 *Would* you *volunteer to try out a new medicine?*

E Producing and selling the medicine

Once the medicine has a licence, it can be sold and used generally. This means that ways must be found to make large quantities of the medicine. This can be very complicated and can involve many steps.

In the case of Compound X, the starting point for production is a chemical called para-toluidine. This is a fairly common and readily available chemical. It can be turned to Compound A in five chemical stages. Compound A is then converted to Compound X (Figure 5).

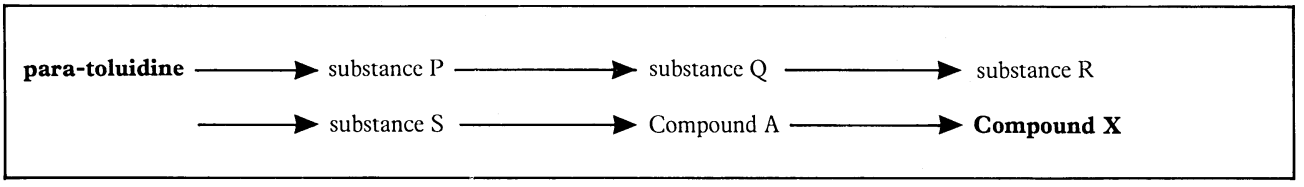

Figure 5 Converting para-toluidine to Compound X

The most difficult stage to carry out is the last one. You will have realized that the only difference between Compound A and Compound X is that Compound X has an extra OH group. To put this on in the right place using a chemical reaction is difficult. Fortunately this step can be done using microbes. Under the right conditions, certain microbes will turn Compound A to Compound X. This is an example of the way **biotechnology** can be used to make substances we need.

Answer question 10.

Question

10 Chemical conversions are never 100 per cent efficient. Suppose each of the six stages in the production of Compound X was only 50 per cent efficient. This means that at each stage, only half the molecules of one substance are turned to the next substance. How many molecules of para-toluidine would you need to start with in order to make 1 molecule of Compound X?

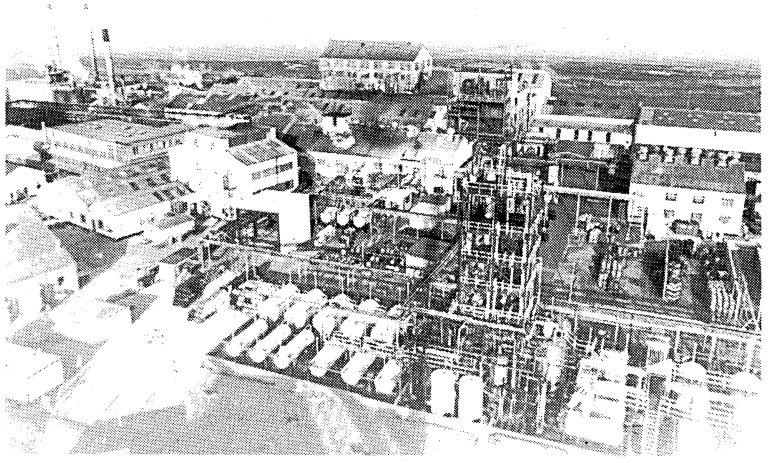

Figure 6 Factories for making pharmaceutical products are often large and complex

Compound X in action

Compound X is widely used to control bilharzia in Africa and South America. A single dose taken by mouth is enough to cure about 85 per cent of patients. Its only side-effect is to cause slight dizziness in some patients. After being cured, patients still run the risk of getting reinfected if they go into contaminated water.

Answer questions 11 to 14. You may like to discuss them in small groups or with the rest of the class.

Questions

11 Pharmaceutical companies make and test many chemical compounds to see if they will make useful medicines. For every compound that becomes a useful medicine, about 10 000 compounds are tested and rejected. Give some of the reasons why a compound may be rejected.

12 Compound X was developed and manufactured in Britain, but it is only used in tropical countries. Why was it not developed by these countries themselves?

13 From what you have heard of Compound X, could it be improved? In what ways could other medicines be made which were better?

14 Developing and testing medicines like Compound X means suffering and loss of life for laboratory animals. Do the benefits of the medicines justify this?